REMARKS

Claims 1-19 are all the claims pending in the application. Applicants amend claims 1 and 12. Support for the amendments can be found in the claims as originally filed, and, *inter alia*, on page 74, lines 1-5 of the specification. Entry is respectfully requested.

The Claims are Patentable Under 35 U.S.C. § 103

Claims 1-11 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Tsugita et al. (Electrophoresis, 1998; hereinafter "Tsugita") in view of Tsugita et al. (Chemistry Letters, 1992; hereinafter "Tsugita '1992") and Covey et al. (U.S. Patent No. 5,952,653; hereinafter "Covey").

Claims 12-19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Tsugita in view of Tsugita '1992, Vogt et al. (Polymer Bulletin, 1996; hereinafter "Vogt") and Covey.

The Examiner takes the position that Tsugita discloses a method of analyzing the C-terminal amino acid sequence of a peptide that discloses several of the features of claims 1-11.

The Examiner concedes that Tsugita uses PFPMe in the cleavage sub-step in the procedure, whereas instant claim 1 recites perfluoroalkanoic acid (PFPA); however, the Examiner states that PFPMe and PFPA have similar structure and functions, and it would allegedly have been obvious to use PFPA in the cleavage sub-step of Tsugita's procedure based on Tsugita '1992 teaching.

The Examiner also concedes that Tsugita does not specifically teach maintaining acetic anhydride in the cleavage sub-step. However, according to the Examiner, since the function of acetic anhydride is to form oxazolone at C-terminal for perfluoroalkanoic acid to act on in the cleavage sub-step, it would have been obvious to recognize that maintaining the concentration of acetic anhydride in the cleavage sub-step may benefit the reaction.

The Examiner also states that Tsugita is silent on using trypsin to cleave the carboxyl side of arginine peptide bond (Arg-C) to improve the accuracy of mass spectrometry analysis.

Covey is cited for disclosing a method of using trypsin to cleave protein and analyzing the result by mass spectrometry. Covey teaches that arginine is basic and picks up a positive charge proton in solution. According to the Examiner, in the mass spectra, the C-terminus fragment shows stronger intensity in anionic species, and all the other tryptic fragments show stronger intensity in cationic species.

Thus, according to the Examiner, it would have been obvious to use trypsin cleavage and mass spectra analysis method as taught by Covey in the second step of Tsugita with a reasonable expectation that trypsin cleavage would increase the accuracy of the mass spectrometry measurement, because the trypsin cleavage reduces the size of peptide for mass spectrometry analysis, and in the mass spectra, the C-terminal peptide fragments obtained by successive release of the C-terminal amino acids would stand out by showing stronger intensity in anionic species, while all the other tryptic fragments would show stronger intensity in cationic species.

As to claims 12-19, Tsugita is cited for disclosing a method of analyzing the C-terminal amino acid sequence of a peptide that allegedly discloses several features claimed in claims 12-19. The Examiner concedes that Tsugita uses PFPMe in the cleavage sub-step in the procedure, whereas claim 12 recites perfluoroalkanoic acid (PFPA). Nonetheless, according to the Examiner, PFPMe and PFPA have similar structure and functions; and it would have been obvious to use PFPA in the cleavage sub-step of the procedure based on teaching of Tsugita '1992 and Tsugita.

The Examiner also concedes that Tsugita does not specifically teach maintaining acetic anhydride in the cleavage sub-step. However, according to the Examiner, since the function of

acetic anhydride is to form oxazolone at C-terminal for perfluoroalkanoic acid to act on in the cleavage sub-step, it would have be obvious that maintaining the concentration of acetic anhydride in the cleavage sub-step may benefit the reaction.

The Examiner states that Tsugita does not teach using polar aprotic solvent to remove water. However, the Examiner believes that using polar aprotic solvent to remove water is known in the art. Also, the Examiner believes that Tsugita does not teach using dipolar-aprotic solvent to swell the gel so that the pretreatment and cleavage sub-step reaction could be carried out on the protein bound to the original gel right after electrophoresis. Rather, Tsugita teaches that the pretreatment and cleavage sub-step of the procedure needs to be carried out in the absence of water. Thus, the target protein has to be extracted from the gel and then dried to remove water or electroblotted to an Immobilon-CD membrane.

Vogt is cited for teaching a new non-aqueous swelling system in which carboxymethyl cellulose (CMC) gel treated with a dipolar aprotic solvent like *N,N*-dimethylacetamide with *p*-toluenesulfonic acid yields a high reactive gel-suspension of the polymer. The dipolar aprotic solvent can remove water from the swollen gel in one step, thus allowing a direct esterification of the hydroxyl group of CMC.

The reason for the rejection is that it would have been obvious to use polar aprotic solvent to remove water and use dipolar aprotic solvent to remove water from the gel carrier bound with the target protein, as taught by Vogt, with reasonable expectation that this would allow Tsugita's procedure to be carried out on the target protein kept on the gel carrier.

Additionally, the Examiner states that Tsugita is silent on using trypsin to cleave the carboxyl side of arginine peptide bond (Arg-C) to improve the accuracy of mass spectrometry analysis.

Covey is cited for disclosing a method of using trypsin to cleave a protein and analyzing the result by mass spectrometry. Covey teaches that arginine is basic and picks up a positive charge proton in a solution, and that the charge difference makes the C-terminus fragment stand out from the other tryptic fragments, because the C-terminus fragment has no arginine at C-terminus and therefore will not have two positive charges.

Thus, according to the Examiner, it would have been obvious to use trypsin cleavage and mass spectra analysis method as taught by Covey in the second step of Tsugita with a reasonable expectation that trypsin cleavage would increase the accuracy of the mass spectrometry measurement, because the trypsin cleavage reduces the size of peptide for mass spectrometry analysis, and in the mass spectra, the C-terminal peptide fragments obtained by successive release of the C-terminal amino acids would stand out by showing stronger intensity in anionic species, while all the other tryptic fragments would show stronger intensity in cationic species.

Applicants respectfully traverse the rejections for the following reasons. Claims 1 and 12 are amended.

Tsugita teaches a process for C-terminal sequencing for a protein comprising the following steps.

The first step of extracting the protein from the protein spot on the polyacrylamide gel is carried out under the following extraction procedure:

The protein spot was excised from the polyacrylamide gel and broken up by the use of a small hand-held homogenizer after the addition to the 500 μL of 6M guanidine-HCl, 0.1% SDS, 0.5 M Bicine, and 4mM EDTA (pH 8.0-8.5). The 6M guanidine-HCl and 0.1% SDS contained in the solution is successfully used to denature the protein, and thus the denatured protein can be

easily extracted from the gel carrier to be collected in the pool of supernatant and two addition washes.

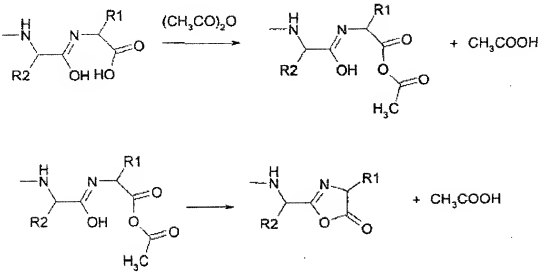
The denatured protein contained in the pooled supernatant is then subjected to purification and separation with a mini-column of C18 silica. The denatured protein isolated by the column separation method is then dried up to use as the dried protein sample.

Tsugita thus fails to teach a process for C-terminal sequencing whereby the reactions for C-terminal stepwise degradation are carried out with the peptide being maintained in a state in which it is bound to the gel carrier.

Tsugita teaches a procedure including reactions for C-terminal stepwise degradation for the dried protein sample comprising the following three reaction sub-steps (i) - (iii):

(i) The first reaction sub-step for acetylation of the N-terminus of the peptide (denatured protein) and formation of an oxazolone at the C-terminal carboxyl group of the peptide (denatured protein):

Acetic anhydride with 20% acetic acid tetrahydrofuran solution and 1% DTT were reacted on the dried sample of peptide (denatured protein) at 60 °C for 10 min. The reactions for the formation of the oxazolone may be carried out by the following reaction scheme:

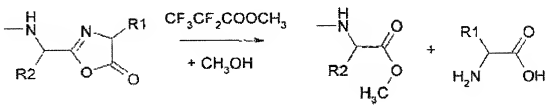


The acetic acid may be used as a catalyst for inducing the conversion of keto-form of the amide moiety into the enol-form.

(ii) The second reaction sub-step for the degradation of the oxazolone-ring to liberate the C-terminal amino acid and to form the esterified peptide is as follows:

The reaction was made with 5% PFPMe (pentafluoropropionic methyl ester: CF_3CF_2-CO-OCH_3) in methanol (CH_3OH) at 5 °C for 15 min.

The degradation of the oxazolone may be carried out by the following reaction scheme:

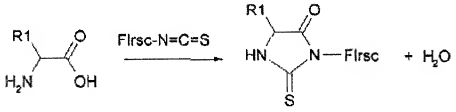


The reaction mechanism may be an alcoholysis to help the catalytic function of PFPMe (pentafluoropropionic methyl ester: CF_3CF_2-CO-OCH_3). The C-terminal amino acid was

liberated to be dissolved in the methanol solution, and thus, the peptidyl reaction product was formed in the shape of esterified peptide.

Therefore, PFPMe (pentafluoropropionic methyl ester: $CF_3CF_2CO\text{-}OCH_3$) was used as a catalytic agent for inducing the solvolysis reaction with use of methanol (CH_3OH) on the oxazolone-ring.

The C-terminal amino acid isolated in the form of free amino acid was modified with fluorescien isothiocyanate, and then analyzed by HPLC. The reaction scheme for the modification with fluorescein isothiocyanate may be shown as follows.

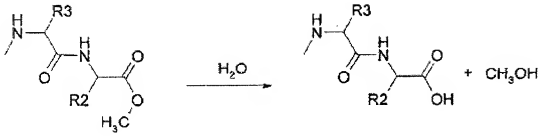


On the other hand, the esterified peptide collected from the reaction solution was subjected to the following final reaction.

(iii) The final reaction sub-step for conversion of the esterified peptide (peptidyl methyl ester) into the peptide with a free carboxyl group at its C-terminus involved:

Using 10 % DMAE aqueous solution at 60 °C for 20 min in the hydrolysis reaction of the ester bond to convert the esterified peptide (peptidyl methyl ester) into the peptide with a free carboxyl group.

The reaction of the hydrolysis of the ester may be carried out by the following reaction scheme:



The peptide with a free carboxyl group was collected from the aqueous solution, and then was dried up to use as a dried peptide sample for the next degradation step.

Accordingly, the peptidyl reaction product (peptide with a free carboxyl group) that is obtained in each of the C-terminal degradation steps is not analyzed by mass spectroscopy.

Indeed, the C-terminal sequence of the denatured protein was made based on HPLC analysis of the C-terminal amino acid (N-(pentafluoropropanoyl) amino acidic methyl ester) obtained in sub-step (ii).

Hence, the dried peptide sample, which has the C-terminal amino acid of -NH-CH(**R2**)-COON to be analyzed in the next step of the C-terminal degradation, should be free from the contamination of the denatured protein that retains un-reacted C-terminal amino acid of -NH-CH(**R1**)-COON.

Tsugita fails to teach any process for the preparation of such a mixture comprising the denatured protein and the series of the peptidyl reaction products (peptide with a free carboxyl group), each of which including a step-wise decreased amino acid sequence. Tsugita by no means uses FAB-MS or MALDI-TOF-MS for the process disclosed in 2.13 C-terminal sequencing.

Tsugita also teaches another process for multi-point C-terminal sequencing (i.e., Chemical specific cleavage and multiple C-terminal sequencing) for a protein as being carried out on a dried protein as well as on the polyacrylamide gel.

The process for the multi-point C-terminal sequencing for the protein sample on the polyacrylamide gel comprises the following steps (a) - (c):

(a) The step of electro-blotting the protein on the polyacrylamide gel to the Immobilon-CD membrane:

At first, the proteins were subjected to one-dimensional or two-dimensional electrophoresis on the polyacrylamide gel. The resulting protein spots on the polyacrylamide gel were electroblotted to the Immobilon-CD membrane and negatively strained. The protein spot identified on the Immobilon-CD membrane was excised and cut into a 1 mm square.

(b) The step of chemical specific cleavage of protein on the blotted membrane :

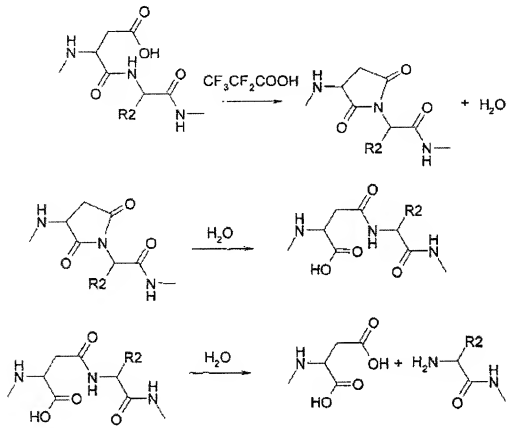
The cut-off square piece of the blotted membrane was put in the small tube and subjected to the specified cleavage reactions. In the specified cleavage reactions, the protein sample was cleaved at the carboxyl side of the aspartyl pepdide bond (Asp-C), or at the amino side of the serine or threonine (Ser/Thr-N) peptide bonds, under the specified cleavage conditions, respectively.

Tsugita employed such a specified cleavage condition for the Asp-C cleavage reaction that a vapor phase reaction was made with a **vapor** generated from a 0.2 % PFPA aqueous solution containing 1 % w/v DTT at 90 °C for 4-16 h.

The group of peptidyl reaction products (peptide fragments) produced in the reaction of cleavage at the carboxyl side of the aspartyl pepdide bond (Asp-C) will consist of the N-terminal

peptide fragment having a newly exposed C-terminal aspartic acid, inner peptide fragments having a newly exposed C-terminal aspartic acid and the C-terminal peptide fragment.

The Asp-C cleavage reaction may be made through the following reaction scheme.

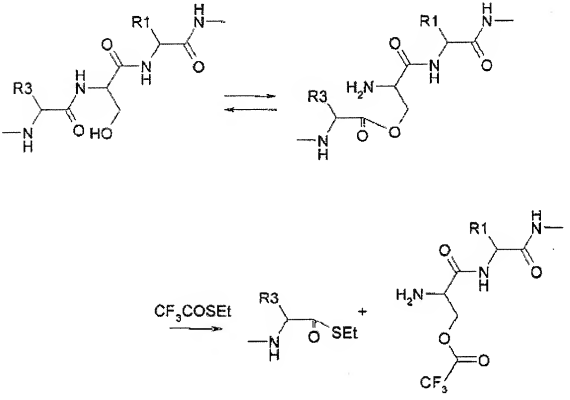


Tsugita employed such a specified cleavage condition for the See/Thr-N cleavage reaction in which a **vapor** phase reaction was made to occur with a vapor of TFASEt (S-Ethyl trifluorothioacetate; $CF_3CO\text{-}S\text{-}CH_2CH_3$) at 30 °C for 24 h or at 50 °C for 6-24 h.

The group of peptidyl reaction products (peptide fragments) produced in the reactions for the cleavage at the amino side of the serine or threonine (Ser/Thr-N) peptide bonds will consist of the N-terminal peptide fragment, inner peptide fragments having a newly exposed N-terminal

Ser/Thr residue and the C-terminal peptide fragment having a newly exposed N-terminal Ser/Thr residue.

The Ser/Thr-N cleavage reaction may be made through the following reaction scheme.



(c) The step of extraction of the peptidyl reaction products from the cut-off square piece of the membrane.

After the specified cleavage reaction, the peptidyl reaction products (peptide fragments) were extracted with 30% and 60% acetonitrile aqueous solutions. The extract was dried and analyzed by FAB-MS or MALDI-TOF-MS.

However, Tsugita fails to teach any process in which chemical specific cleavage was carried out on the protein while maintained in a state of being bound on the polyacrylamide gel in place of the protein on the blotted membrane.

In view of the foregoing, Tsugita also fails to suggest C-terminal stepwise degradation or for chemical specific cleavage, which is carried out on the peptide (denatured protein) being maintained in a state in which it is bound on a gel carrier, such as polyacrylamide gel.

Such process is suitable for use in the preparation of a mixture comprising the denatured protein and the series of the peptidyl reaction products (peptide with a free carboxyl group), each of the products having a step-wise decreased amino acid sequence.

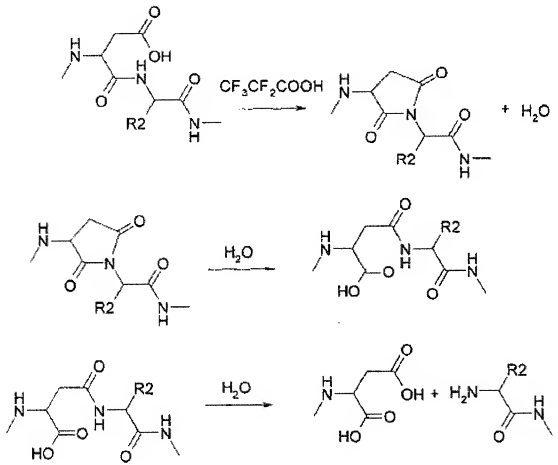
Tsugita also fails to provide any suggestion as to whether or not PFPA, which is suitably used in the vapor phase reaction for the Asp-C cleavage reaction, would be employed as a reactant for the liquid phase reaction for degradation of the oxazolone-ring, in place of PFPMe. The function of PFPMe used in the liquid phase reaction for degradation of the oxazolone-ring is quite different from the catalytic function of PFPA used in the vapor phase reaction for the Asp-C cleavage reaction. Hence, there is no reason to believe that PFPA would have a similar function to that of PFPMe used in the liquid phase reaction for degradation of the oxazolone-ring.

Additionally, Tsugita teaches a process for C-terminal sequencing at multiple sites for the protein, the process being carried out on the dried protein sample, as well as the protein sample blotted on Immobilon-CD membrane. (See 3.4 C-terminal sequencing at multiple sites)

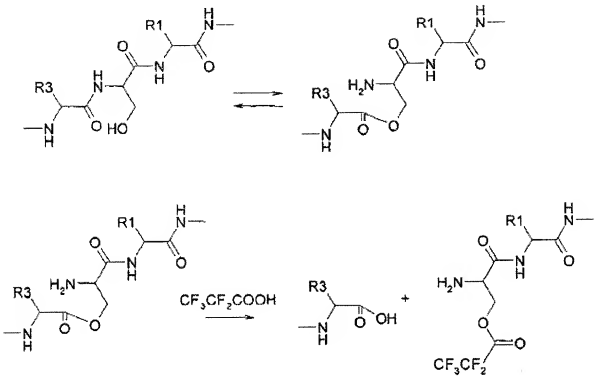
In the process for C-terminal sequencing at multiple sites, the dried protein sample or the protein sample blotted on Immobilon-CD membrane was reacted with the vapor of concentrated perfluoric acid, i.e. a vapor from a 90 % PFPA aqueous solution containing 1 % DTT at 90 °C

for 2-16 h. The reaction with the aqueous vapor from 90 % PFPA aqueous solution at 90 °C for 2-16 h provided cleavage at the C-side of aspartic acid (Asp-C cleavage reaction) and cleavage the N-side of serine/threonine (Ser/Thr-N cleavage reaction), and simultaneous successive truncation at the C-termini of the cleaved fragments.

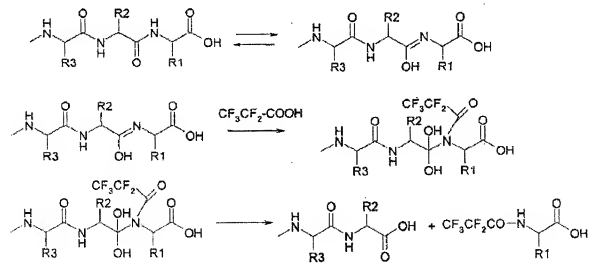
The Asp-C cleavage reaction may be made through the following reaction scheme.



The Ser/Thr-N cleavage reaction may be made through the following reaction scheme.



The reaction of the simultaneous successive truncation at the C-termini of the cleaved fragments may be made through the following reaction scheme.



In the reaction of truncation at the C-terminus of the cleaved fragment, the vapor of PFPA (CF_3CF_2COOH) may be used as a reagent.

As shown in Table 3, the C-terminal **Pro** of the fragment of SPRESLSAL**P** was successfully truncated by using the reaction condition, and thus, the formation of oxazolone-ring is by no means contained in the reaction path. Indeed, as Pro has a cyclic form, any oxazolone-ring can never be formed from Pro residue at the C-terminus of the peptide fragment.

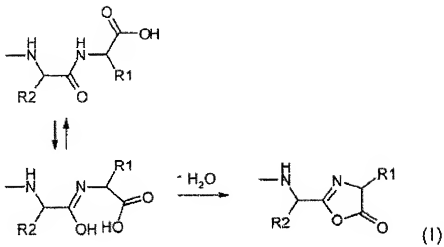
Therefore, the reaction scheme of the process used for C-terminal sequencing at multiple sites is quite different from the reaction scheme of the process as claimed in Claims 1-11.

Accordingly, Tsugita fails to teach a process for preparing a mixture containing a series of peptidyl reaction products by chemically releasing the C-terminal amino acids successively, in which the oxazolone-ring is formed from the C-terminal amino acid, and any chemical cleavage of the peptide is prevented.

In contrast, the process for releasing the C-terminal amino acids successively from the peptide of the present invention is carried out through the following reaction schemes:

(I) reaction for formation of 5-oxazolone ring:

The reaction for formation of 5-oxazolone ring is expressed on the whole by the following reaction scheme (I):

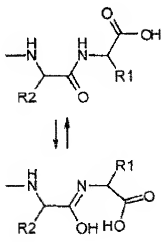


(I)

The reaction of scheme (I) consists of the following two stages (Ia) and (Ib).

(Ia) keto-enol tautomerism:

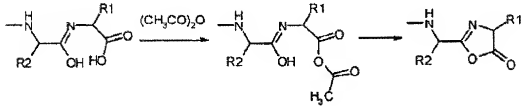
The perfluoroalkanoic acid contained in the mixed solution of the alkanoic acid anhydride and the perfluoroalkanoic acid dissolved in the dipolar aprotic solvent is allowed to act as a proton donor on the dried peptide at the stage of keto-enol tautomerism, as shown in the following reaction scheme (Ia):



(Ia)

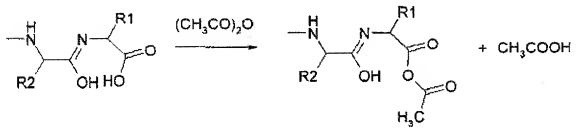
(Ib) formation of the activated C-terminal carboxyl group and formation of the intramolecular ester bond (formation of the 5-oxazolone ring):

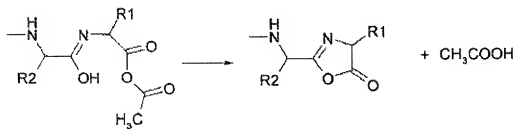
The alkanoic acid anhydride is used as a reagent for formation of the activated C-terminal carboxyl group. The activated C-terminal carboxyl group is reacted with the hydroxyl group to form the 5-oxazolone ring.



(Ib)

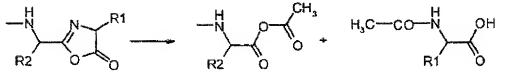
The following is a detailed reaction scheme of the stage (Ib):





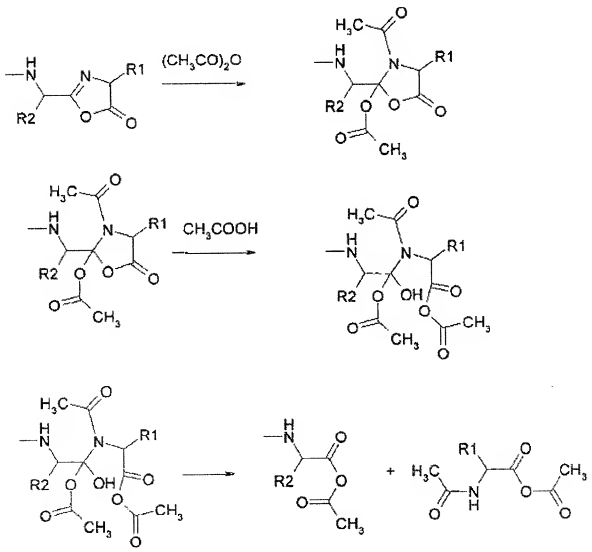
(II') separation of the C-terminal amino acid and formation of the reaction intermediate for the next stage:

The alkanoic acid anhydride is used as a reagent for the addition reaction on the double bond of >C=N- type of the 5-oxazolone ring. The degradation of the 5-oxazolone ring is made via such a reaction as shown by the following reaction scheme (II'):



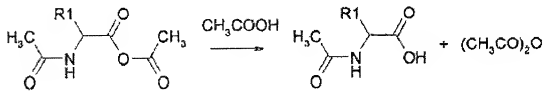
(II')

The following may be a detailed reaction scheme of the stage (II').



The alkanoic acid, which is a by-product from the alkanoic acid anhydride formed at the stage (Ia) is used as a reagent at the second reaction for opening of the ester bond therein.

In addition, the alkanoic acid also reacts on the derivative of the C-terminal amino acid having acid anhydride form, and thereby the C-terminal acid anhydride form thereof is converted into the C-terminal carboxyl group.



The peptidyl reaction product having the activated C-terminal carboxyl group of the third reaction is ready for the formation of the 5-oxazolone ring at the next stage.

The considerable variation of the reaction speeds of those stages is used to prepare a mixture comprising the original peptide and the series of peptidyl reaction products produced therefrom.

The reaction schemes used in the process for releasing the C-terminal amino acids successively from the peptide of the present invention are clearly different from those used in the process for C-terminal stepwise degradation or in the process for C-terminal sequencing at multiple sites disclosed in Tsugita.

Tsugita '1992 teaches a reaction of pentafluoropropionic anhydride (PFPAA: $(CF_3CF_2\text{-}CO)_2O$) **vapor** on polypeptide, in which a vapor phase reaction is made with the pentafluoropropionic anhydride (PFPAA: $(CF_3CF_2\text{-}CO)_2O$) vapor at low temperature, e.g. -18°C. Tsugita '1992 also suggests a reaction scheme for the C-terminal successive degradation of polypeptides, in which the vapor of PFPAA ($(CF_3CF_2\text{-}CO)_2O$) from 10% PFPAA in acetonitrile

(CH_3CN) is used as a reagent for the sub-step of formation of oxazolone from the C-terminal amino acid of the peptide, and the vapor of PFPA derived from PFPAA is used as a reagent for the sub-step of degradation of the oxazolone ring.

In view of this suggested reaction scheme, Tsugita '1992 fails to suggest that PFPA may be used as a catalytic agent inducing the degradation of the oxazolone ring rather than a reagent involved in the degradation of the oxazolone ring. Tsugita '1992 also fails to suggests that PFPA (CF_3CF_2-COOH) may be used as a catalytic agent inducing the degradation of the oxazolone ring by alcoholysis with methanol in place of PFPMe (CF_3CF_2-$COOCH_3$).

Covey et al. teaches a procedure of enzymatic digestion of the long peptide by trypsin to cleave the long peptide into tryptic fragments. Covey et al also teaches a double charge rule that the tryptic fragment having Arg or Lys at the C-terminus thereof will be doubly positively charged by using an Ion spray process for Ion Evaporation Mass Spectrometry, but that there are three exceptions to the double charge rule as follows:

i) First exception: such a tryptic fragment having other amino acid than Arg or Lys at the C-terminus thereof will only be singly charged by using Ion spray process for Ion Evaporation Mass Spectrometry;

ii) Second exception: such a tryptic fragment having an amino terminus which is carboxylated or blocked (e.g. N-acylation at the N-terminus) will only be singly charged by using Ion spray process for Ion Evaporation Mass Spectrometry; and

iii) Third exception: such a tryptic fragment having Arg or Lys at the C-terminus thereof and containing an internal His will be triply charged in small percentage, bul will be doubly charged in most percentage.

However, Covey et al. fails to suggest whether or not such a double charge rule would be also observed for MALDI-TOF-MS or FAB-MS. Covey et al. fails to provide any suggestion as to the intensity of a singly positive charged ion from the tryptic fragment having Arg or Lys at the C-terminus thereof to be measured by MALDI-TOF-MS; and fails to provide any suggestion as to the intensity of a singly negative charged ion from the tryptic fragment having amino acids other than Arg or Lys at the C-terminus thereof to be measured by MALDI-TOF-MS.

Covey et al. thus also fails to suggest that a singly positive charged ion from the tryptic fragment having Arg or Lys at the C-terminus thereof may show stronger intensity in cationic species spectrum measured by MALDI-TOF-MS.

As to Claims 12-19, Applicants submit that Tsugita fails to teach or suggest any process in which chemical specific cleavage was carried out on the protein being maintained in a state that it is bound on the polyacrylamide gel in place of the protein on the blotted membrane.

Accordingly, Tsugita fails to provide any suggestion as to such a process for C-terminal stepwise degradation or for chemical specific cleavage, which is carried out on the peptide (denatured protein) being maintained in a state of being bound on a gel carrier, such as polyacrylamide gel.

The process as claimed in Claims 12-19 also employs a liquid phase reaction in place of a vapor phase reaction. As submitted herein, the reaction schemes used in the claimed process for releasing the C-terminal amino acids successively from the peptide are different from those used in the process disclosed in Tsugita.

As noted, Tsugita '1992 teaches a reaction of pentafluoropropionic anhydride ($(CF_3CF_2\text{-}CO)_2O$) **vapor** on polypeptide, in which a vapor phase reaction occurs with the pentafluoropropionic anhydride ($(CF_3CF_2\text{-}CO)_2O$) vapor at low temperature (-18 °C).

However, Tsugita '1992 fails to provide any suggestion as to the reaction condition used for the liquid phase reaction in place of the reaction condition used for the vapor phase reaction in the process for C-terminal stepwise degradation disclosed in Tsugita.

Vogt et al. teaches a process for the preparation of a high reactive gel-suspension of carboxymethyl cellulose (CMC), in which the polymer (carboxymethyl cellulose) is treated in a dipolar-aprotic solvent, such as N,N-dimethylacetamide and dimethylsulfoxide (DMSO), with p-toluene-sulfonic acid. Vogt et al. also assumes that activation (swelling in the dipolar-aprotic solvent) is achieved via an interaction between the carboxylate groups (-CH_2-COONa) of the NaCMC and HO_3S-groups of the p-toluene-sulfonic acid with a rapid exchange of the acidic hydrogen as well as an interaction of the lipophilic toluene unit of the p-toluene-sulfonic acid with the solvent.

Accordingly, Vogt et al. fails to teach any process for the preparation of a gel-suspension of CMC in the dipolar-aprotic solvent without p-toluene-sulfonic acid.

Further, Vogt et al. discloses that an effective method for activation of CMC is precipitation of an aqueous solution of CMC by N,N-dimethylformamide (DMF), and the removal of the water from the swollen gel by repeated distribution under reduced pressure. This disclosure may indeed indicate that N,N-dimethylformamide (DMF) could never remove water from the water-swollen gel of CMC. Vogt et al. also discloses that other acids, like methane sulfonic acid, trifluoroacetic acid and monochloroacetic acid do not swell CMC to a comparable extent. Vogt et al. notes that polysaccharides with the polymer backbone-bound carboxy groups like sodium alginate, sodium pectinate, and 6-carboxy cellulose, also do not swell in the manner described for CMC.

In view of the foregoing, Vogt et al. fails to provide any suggestion as to whether or not the combined use of the dipolar aprotic solvent, with acid other than p-toluene-sulfonic acid (e.g., perfluoroalkanoic acid), could be successfully applied in the preparation of a non-aqueous swelling gel of a polymer other than CMC. Vogt et al. further fails to suggest whether the use of the dipolar-aprotic solvent without p-toluene-sulfonic acid could be successfully applied.

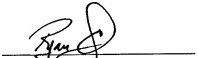
For at least the foregoing reasons, none of the Tsugita, Tsugita '1992, Covey or Vogt, alone or in combination, would have rendered obvious the features of any of the pending claims.

Withdrawal of the rejections are earnestly solicited.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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